REMARKS

Reconsideration and withdrawal of the rejections in the outstanding Office Action are respectfully requested in view of the foregoing amendments and the following remarks.

Summary of Status of Amendments and Office Action

In the present Amendment, claims 1-8 have been amended, and claims 9-10 have been added, with claims 1 and 10 being independent claims. Claims 1-10 will remain pending and under consideration.

Applicants note that claims 1-8 have been amended to recite active processes involved in the method of selecting trial compounds. Support for the amendments may be found throughout Applicants' originally filed disclosure, especially at pages 4-5 and 11-14. No new matter is added.

Claims 1-3 have been amended in response to the Examiner's objections to the claims.

Reconsideration and allowance of the application are respectfully requested.

Claim of Priority

Applicants express appreciation for the acknowledgement of the claim of priority to Japanese Application No. 7-294189, filed November 13, 1995, as well as receipt of the certified copy of the Japanese application filed in parent Application No. 09/068,459.

Drawings and Information Disclosure Statement

Applicants express appreciation for acceptance of the Drawings filed November 14, 2001, and consideration of Information Disclosure Statements filed November 14, 2001, and July 3, 2002, by including initialed copies of the Forms PTO-1449 submitted therein with the Office Action.

The Office Action asserts that the Information Disclosure Statement filed November 14, 2001, fails to comply with the provisions of 37 C.F.R. 1.97, 1.98, and MPEP 609 because copies of document No. 5 by Tomioka et al., document No. 9 by Yamada et al., and two foreign documents (WO 96/13785 and 97/24301) were not found in the Office's file wrapper of the parent application.

Applicants note that Yamada et al., WO 96/13785, and WO 97/24301 were made of record and considered by initialed copies of the Forms PTO-1449 in the parent application by the Examiner. Copies of the initialed Forms PTO-1449 are enclosed herewith. Also, Applicants note that Tomioka et al., even though it is in the Japanese language, was made of record in the parent application in the English-language International Search Report of corresponding International Application WO 97/18180. Accordingly, the requirement for a concise explanation of relevance of Tomioka is satisfied by the English-language International Search Report, because the Report indicates the degree of relevance of Tomioka found by a corresponding foreign office. See MPEP 609(III)(A)(3).

In order to assist the Examiner, Applicants have enclosed copies of the four previously cited documents, and a copy of WO 97/18180 with the International Search Report attached. Applicants also attach a new Form PTO-1449 listing the four documents

not yet considered by the Examiner, and respectfully request that the Examiner indicate that the documents have been considered by initialing a copy of the Form and returning a copy to the Applicants with the next PTO correspondence.

Applicants do not believe that any additional fees are required to have these previously cited documents made of record and considered in the current application. However, if a fee is required, the Office is hereby authorized to charge any necessary fees for entry and consideration of the cited documents to Deposit Account No. 19-0089.

Response to Claim Objections

Claims 1-3 are objected because the term "containing" is open claim language, the phrase "at least" is redundant and should be deleted, and the phrase "by using a computer" is awkward.

In response, Applicants note that they have amended claim 1 and the objections are rendered moot.

Response to 35 U.S.C. § 101 Rejection

Claims 1-7 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter.

In response, Applicants note that claim 1 has been amended to recite "wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer." One of skill in the art would

understand from reading the specification that the method claimed for selecting a lead-compound clearly produces a concrete, tangible, and useful result.

In addition, Applicants note that claims 1-8 have been amended to recite at least one active transforming process, including reciting at least one process of selecting trial compounds. For at least these reasons, Applicants submit that the claims are directed to statutory subject matter.

Accordingly, Applicants respectfully request that the rejection of claims 1-7 under 35 U.S.C. § 101 be withdrawn.

Response to 35 U.S.C. § 112 Rejections

Enablement rejection

Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement because the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action asserts that the claims are not enabled for selection of a lead-candidate compound which binds to any type of biopolymer because neither the specification nor "prior art" teach specific parameters for selection of a compound(s) which bind to any biopolymer. The Office Action asserts that the specification does not teach particular conditions which must be met to select a compound as a "lead-candidate." For instance, the Office Action asserts that the specification does not teach how to single out any

particular compound as a "better" ligand than the others, or which binds more tightly than another.

Further, the Office Action asserts that the claims are not enabling for identifying compounds which bind to any other type of biopolymer other than compounds which may bind to proteins such as dihydrofolate reductase. The Office Action asserts that the specification teaches how to determine or identify compounds likely to bind to a protein, but the claims are broadly directed to a selection of lead-candidate compound capable of binding to any type of biopolymer.

In response, Applicants respectfully submit that one of ordinary skill in the art would know that the specification enables the claimed method for selecting lead-candidate compounds from a compound database. However, solely for the purpose of advancing prosecution of the present application, claim 1 has been amended to recite a method for selecting at least one lead-candidate compound capable of binding to a biopolymer, wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer, comprising: obtaining a compound database comprising information on atomic types and covalent bonds of compounds in the database, selecting at least one query molecule capable of binding to the biopolymer, and selecting at least one trial compound by matching at least one query molecule with trial compounds stored in the database based on information on atomic types and covalent bonds of the at least one query molecule. The specification provides sufficient disclosure to enable one of ordinary skill in the art to select lead-candidate compounds capable of binding to a

biopolymer from a compound database comprising information on atomic types and covalent bonds of compounds. Applicants note that it is within the scope of common technical knowledge of one of ordinary skill in the art following the guidance set forth in Applicants' specification, especially from Example 1 and Fig. 3 of compounds which bind to proteins such as dihydrofolate reductase, that other compounds may be identified which bind to other biopolymers using the claimed method because biopolymers are clearly defined in the specification at page 1, paragraph 2 as being "a physiologically active compound [that] interacts specifically with a certain polymer in the living body (it is herein referred to as a "biopolymer[,]" or "receptor" as the case may be"). In addition, Figs. 1 and 2 represent algorithms using the claimed method for selecting lead-candidate compounds capable of binding to a biopolymer from a compound database comprising information on atomic types and covalent bonds of compounds.

Furthermore, pages 4-5, and 7-17 of the instant specification disclose selection of lead-candidate compounds by matching at least one query molecule capable of binding to the biopolymer with compounds stored in the database based on information regarding atomic types and covalent bond mode of the query molecules. The structures of the query compounds may be constructed by an automatic construction method by calculations based upon the three-dimensional structure information for the biopolymer and/or known ligands. The structural information may then be used for subsequent screening as demonstrated on page 17 of the instant specification in order to reduce the number of query molecules using reduction criteria such as molecular

skeletons, flexibility of molecules, and binding schemes to ligand binding sites. Additionally, when molecular structures are used as query molecules, criteria including intramolecular and intermolecular energy, energy of the whole system, number of hydrogen bonds, hydrogen bonds to specified locations, formation of ionic bonds, and number of rings may be used. One of ordinary skill in the art can readily understand from the guidance set forth in the specification, that lead-candidate compounds may be selected to bind to a biopolymer using the claimed method for selecting lead-candidate compounds capable of binding to a biopolymer from a compound database comprising information on atomic types and covalent bonds of compounds.

In addition, new claim 9 recites calculating the interaction energy between the at least one trial compound and the biopolymer. One of skill in the art reading the specification would understand that the specification enables the full scope of the claim. For example, the methods of Tomioka et al. disclosed at pages 13-14 enable calculation of such interaction energies between any selected trial compound and the biopolymer.

Therefore, Applicants' claims are enabled, and respectfully request that the rejection of claims 1-8 under 35 U.S.C. §112, first paragraph be withdrawn.

Indefiniteness rejection

Claims 1-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action asserts that claims 1-2 provides

for the use of a computer, but does not clearly set forth steps involved in the method/process so that it is unclear as to what method/process that Applicants intend to encompass. The Office Action asserts that claims 1-2 are directed to methods of selecting compounds, but fail to recite any actual selection step(s), and that it is unclear as to the level of modification intended by the phrase "modified to an extent." The Office Action also asserts that the phrase "and the like" in claim 2 is indefinite because the elements are not actually disclosed.

Furthermore, claim 6 is rejected as being indefinite because the Office Action asserts that the claim is limited to a step (a) to comprise steps (c) and (d), but not step (b) is recited. Claim 8 is rejected as being indefinite because the Office Action asserts that the claim limits the method of claim 3 to further comprise a "third screening" comprising step (f) and/or a step (g), but it is unclear by what is meant by "third screening."

In response, Applicants respectfully submit that the claims pending prior to the present amendment definitely define what Applicants consider to be their invention. However, in order to advance prosecution of the present application, and without acquiescence, Applicants have amended claim 1 to recite a method for selecting at least one lead-candidate compound capable of binding to a biopolymer, wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer, comprising: obtaining a compound database comprising information on atomic types and covalent bonds of compounds in the database, selecting at least one query molecule capable of binding to

the biopolymer, and selecting at least one trial compound by matching at least one query molecule with trial compounds stored in the database based on information on atomic types and covalent bonds of the at least one query molecule.

Additionally, Applicants have amended claims 2-8 to more clearly define features of the present invention. In particular, claim 2 has been amended to further recite modifying the structure of the at least one query molecule by an automatic structure construction method. Claim 6 has been amended to further recite estimating binding schemes of the trial compounds to the biopolymer based on the binding schemes of at least one query molecule to the biopolymer; calculating at least one parameter relating to interaction between the trial compounds and the biopolymer; and screening the trial compounds based on the parameters. Claim 8 has been amended to recite screening trial compounds based on at least one parameter selected from number of atoms, number of bonds, number of ring structures, number of atoms for each atomic type, and molecular weight.

Applicants note that one of ordinary skill in the art would understand from reading the specification, especially at pages 4-5, 7-17, and Figs. 1 and 2, that criteria recited in the claimed method for selecting a lead-compound is clear and definite.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-8 under 35 U.S.C. §112, second paragraph.

Response to 102(b) Rejection

Desjarlais

Claims 1-8 are rejected under 35 U.S.C. §102(b) as anticipated by Desjarlais et al. (Proc. Nat. Acad. Sci. USA, Vol. 87, pp. 6644-6648 (1990)) (hereinafter "Desjarlais"). The Office Action asserts that Desjarlais discloses a computational method for structure based drug design of inhibitors (lead-candidate compounds) of HIV-1 protease (biopolymer) and obtains three-dimensional information for both the protease and the drug candidates from a database and fits the drug candidates into a model of the inhibitor binding site of the protein.

Applicants note that Desjarlais is directed to using a structure-based computer-assisted search in which the computer creates a negative image of the active site cavity using the crystal structure of the HIV-1 protease, and the image was compared for steric complementarity with 10,000 molecules of the Cambridge Crystallographic Database (see Abstract of Desjarlais). The emphasis of the method disclosed in Desjarlais is on the complex steric features of macromolecular surface (see paragraph 2, Introduction of Desjarlais). Desjarlais discloses a DOCK program which uses interactive inspection of the structures in order to characterize the shape of invaginations and grooves that form the active sites and recognition surfaces of biological macromolecules (see paragraph 2, Introduction of Desjarlais). The DOCK program proposes specific orientations of a given template molecule in the active site, but the proposals cannot be considered as predictions because molecular energies are not evaluated (see page 6645, second full paragraph of Desjarlais). Additionally, the DOCK program disclosed in Desjarlais constructs a negative image of the active site from x-ray coordinates, and the molecular surface generated by the program is

composed of 34 intersecting spheres whose centers are used with a matching algorithm to determine which small molecule candidates could be placed within the site. The DOCK program ranks the putative ligands based on a simple function of the interatomic distances. As a result, the DOCK program investigates the orientations within the site for each molecule, and saves the orientation with the highest score.

In contrast to the steric complementarity and scoring system based on interatomic distances used by the DOCK program disclosed in Desjarlais, Applicants' present invention is directed to a method for selecting at least one lead-candidate compound capable of binding to a biopolymer, wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer, comprising: obtaining a compound database comprising information on atomic types and covalent bonds of compounds in the database, selecting at least one query molecule capable of binding to the biopolymer, and selecting at least one trial compound by matching at least one query molecule with trial compounds stored in the database based on information on atomic types and covalent bonds of the at least one query molecule. Such considerations or criteria for binding schemes are discussed throughout the specification, especially at the paragraph bridging pages 15 to 16 of the present specification include intramolecular and intermolecular energy, energy of the whole system, number of hydrogen bonds, hydrogen bonds to specified locations, formation of ionic bonds, and number of rings. Furthermore, the method taught by Desjarlais fails to use a query molecule capable of binding to the protein, and as a result, the method fails to perform matching of the

database molecule to the query molecule.

Because Desjarlais discloses screening of database compounds based on the fitting of each compound to the "negative image" of a target protein which is represented as a group of spheres contacting the protein surface, there is nothing in Desjarlais that teaches the claimed method for selecting at least one lead-candidate compound capable of binding to a biopolymer, wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer, comprising: obtaining a compound database comprising information on atomic types and covalent bonds of compounds in the database, selecting at least one query molecule capable of binding to the biopolymer, and selecting at least one trial compound by matching at least one query molecule with trial compounds stored in the database based on information on atomic types and covalent bonds of the at least one query molecule.

Moon

Claims 1-8 are rejected under 35 U.S.C. §102(b) as anticipated by Moon et al. (Tetrahedron Computer Methodology, Vol. 3, No. 6C, pp. 697-711 (1990)) (hereinafter "Moon"). The Office Action asserts that Moon discloses GROW, a computer-based method for identifying lead compounds that bind to the receptor of a known protein.

Moon uses a scoring system and compares the highest scoring conformation generated by the GROW program (see Fig. 1, page 699 of Moon). Moon is directed to using a combination of 3D database searching and *de novo* construction methods

which uses a tree-based conformational search over a library of fragments, and a form of simulated annealing which allows designed ligands to crawl around the binding site even as their structures are changing in order to determine substructure and superstructure scoring (see Abstract). For the *de novo* design method, Moon discloses a GROW program which uses three sets of input data: an atomic coordinate file for the target receptor, a user-supplied "seed" location for growth initiation, and a library of conformations of amino acids which is precalculated (page 698, fourth to sixth paragraphs of Moon). Each fragment is a "discretized" approximation of the continuous space accessible to the flexible building blocks (page 698, fourth full paragraph of Moon). The GROW program disclosed in Moon superimposes on the seed amide the amide group of every template in the library, and each construct is evaluated by a molecular mechanics-based scoring function (page 698, seventh full paragraph of Moon). All but the highest scoring "n" is pruned off the tree, and the process of fragment attachment, scoring, and pruning is repeated until the user-specified peptide length is achieved.

Furthermore, the GROW program disclosed by Moon is a method of *de novo* design of a ligand molecule that may have the ability to bind to a target protein. The *de novo* design method belongs to a different technical field from that of the database search methods to which the present claimed method belongs. The GROW program merely treats peptidic fragments to construct a peptide ligand. The GROW program cannot be used for searching a database containing various kinds of compounds having a variety of chemical structures not limited to peptides. The "seed structure" of

GROW is used as a starting point of the structure construction, and is not an equivalent of the "query molecule" of the present claimed invention. There is nothing in Moon that teaches or suggests the claimed method for selecting at least one lead-candidate compound capable of binding to a biopolymer, wherein the lead-candidate compound is a candidate for use as a physiologically active compound when the compound interacts specifically with the biopolymer, comprising: obtaining a compound database comprising information on atomic types and covalent bonds of compounds in the database, selecting at least one query molecule capable of binding to the biopolymer, and selecting at least one trial compound by matching at least one query molecule with trial compounds stored in the database based on information on atomic types and covalent bonds of the at least one query molecule.

Therefore, because neither Desjarlais nor Moon teaches or suggests the Applicants' claimed invention, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-8 under 35 U.S.C. §102(b).

CONCLUSION

For the foregoing reasons, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested.

If the Examiner has any questions, or wishes to discuss this matter, the Examiner is respectfully invited to contact the undersigned at the below-listed telephone number.

Should the Examiner have any questions, please contact the undersigned at the telephone number provided below.

Respectfully submitted,
A. ITAI et al.

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